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Dated: January 25, 2011
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: RUJ-001CNRCE2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ralph Steinman *et al.*

Application No.: 09/586,704 Art Unit: 1644

Filed: June 5, 2000 Examiner: Ronald B. Schwadron

For: IDENTIFICATION OF DEC, A RECEPTOR WITH C-TYPE LECTIN DOMAINS, NUCLEIC ACID ENDODING DEC, AND USES THEREOF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

Appellants hereby appeal the final decision of the Examiner in the above-identified application rejecting the subject matter of the pending claims. For the reasons set forth in this Brief, Appellants respectfully request the Board of Patent Appeals and Interferences reverse the Examiner's final rejection of the claimed subject matter. An Amendment pursuant to 37 C.F.R. § 41.33 is submitted herewith to cancel claims 44-45 and reduce the issues on appeal. A Request for Extension of Time for one month is submitted herewith.

This brief contains items under the following headings as required by 37 C.F.R. §41.37 and M.P.E.P. §1205.2:

Appendix A Claims
Appendix B Evidence
Appendix C Related Proceedings

I. REAL PARTY IN INTEREST

The real parties in interest in the above-identified application are Rockefeller University, the assignee of the application, and Celldex Therapeutics, Inc., the licensee of the application.

II. RELATED APPEALS AND INTERFERENCES

An Appeal Brief was filed in U.S.S.N.: 09/925,284 (having a filing date of August 9, 2001) on November 22, 2010. No related interferences are known to Appellants, which will directly affect, or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 22-23, 26-30, and 35-36, 38-40, and 42-45 were pending in this application. Claims 22-23 and 29-30 have been withdrawn from consideration.

Claim 44 and 45 are canceled per the Amendment to Accompany Appeal Brief pursuant to 37 C.F.R. § 41.33 submitted herewith. Claims 26-28, 35-36, 38-40, and 42-43 are on appeal and are set forth in the Claims Appendix (Appendix A).

IV. STATUS OF THE AMENDMENTS

An Amendment After Final was filed by Appellants on October 25, 2010. As indicated in the Advisory Action dated November 5, 2010, Appellants' Amendment After Final has been entered. Additionally, an Amendment pursuant to 37 C.F.R. § 41.33 is submitted herewith to cancel claims 44-45 and reduce the issues on appeal. Accordingly, claims 26-28, 35-36, 38-40, and 42-43 are on appeal and are set forth in the Claims Appendix (Appendix A).

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 26-28

Claim 26 is drawn to a vaccine for inducing an immune response comprising an immune stimulator and an antigen conjugated to an anti-human DEC-205 antibody or an anti-murine DEC-205 antibody reactive with a human DEC-205 protein comprising

the human DEC-205 protein as set forth in SEQ ID NO: 1. The amino acid sequence of SEQ ID NO: 1 corresponds to a partial (C-terminal) sequence of human DEC-205. Support for independent claim 26 can be found at least, for example, at page 3, lines 15-19; page 5, lines 13-23; page 7, lines 1-12; page 10, line 20 through page 11, line 14; page 55, line 30 through page 56, line 23; page 62, line 26 to page 63, line 15 and page 67, lines 15-21 of the specification as originally filed.

Dependent claims 27 and 28 on appeal do not stand or fall together with independent claim 26, or with each other, because the scope of each dependent claim differs from the independent claim, and from each other. In particular, dependent claims 27-28 include additional features not required by independent claim 26. Specifically, dependent claim 27 specifies that the antigen is selected from the group consisting of a virus, a bacterium, a parasite, and a tumor. Support for dependent claim 27 can be found, at least, for example, in original claim 27, at page 7 (lines 5-6); and page 46 (lines 14-15) of the specification as originally filed. Dependent claim 28 specifies that the immune stimulator is selected from the group consisting of a cytokine, a lymphokine, and an adjuvant. Support for dependent claim 28 can be found, at least, for example, in original claim 28 and at page 7 (lines 6-8); page 18 (lines 1-4); page 46 (lines 6-15) of the specification as originally filed. Accordingly, the scope and limitations of claims 27 and 28 differ from claim 26, and thus the inquiry as to whether these claims are properly enabled and sufficiently described also differs from claim 26.

Claims 35-36 and 38-39

Independent claim 35 on appeal is drawn to a vaccine for inducing an immune response comprising an immune stimulator and an antigen conjugated to an anti-human DEC-205 antibody, wherein the antibody is reactive with the amino acid sequence as set forth in SEQ ID NO: 1. As noted above, the amino acid sequence of SEQ ID NO: 1 corresponds to a partial (C-terminal) sequence of human DEC-205. Support for independent claim 35 can be found at least, for example, at page 3, lines 15-19; page 5, lines 13-23; page 7, lines 1-12; page 10, line 20 through page 11, line 14; page 55, line 30 through page 56, line 23; page 62, line 26 to page 63, line 15 and page 67, lines 15-21 of the specification as originally filed.

Independent claim 36 on appeal is drawn to a vaccine for inducing an immune response comprising an immune stimulator and an antigen conjugated to an anti-mouse DEC-205 antibody, wherein the antibody is reactive with the amino acid sequence as

set forth in SEQ ID NO: 1. As noted above, the amino acid sequence of SEQ ID NO: 1 corresponds to a partial (C-terminal) sequence of human DEC-205. Support for independent claim 36 can be found at least, for example, at page 3, lines 15-19; page 5, lines 13-23; page 7, lines 1-12; page 10, line 20 through page 11, line 14; page 55, line 30 through page 56, line 23; page 62, line 26 to page 63, line 15 and page 67, lines 15-21 of the specification as originally filed.

Dependent claims 38 and 39 on appeal do not stand or fall together with independent claims 35 and/or 36, or with each other, because the scope of each dependent claim differs from the independent claims, and from each other. In particular, dependent claims 38-39 include additional features not required by independent claims 35 or 36. Specifically, dependent claim 38 specifies that the immune stimulator is selected from the group consisting of a cytokine, a lymphokine, and an adjuvant. Support for dependent claim 38 can be found, at least, for example, in original claim 28 and at page 7 (lines 6-8); page 18 (lines 1-4); page 46 (lines 6-15) of the specification as originally filed. Dependent claim 39 specifies that the antigen is selected from the group consisting of a virus, a bacterium, a parasite, and a tumor. Support for dependent claim 39 can be found, at least, for example, in original claim 27, at page 7 (lines 5-6); and page 46 (lines 14-15) of the specification as originally filed. Accordingly, the scope and limitations of claims 38 and 39 differ from claims 35 and 36, and thus the inquiry as to whether these claims are properly enabled and sufficiently described also differs from claims 35 and 36.

Claims 40 and 42-43

Independent claim 40 on appeal is drawn to a vaccine for inducing an immune response comprising an immune stimulator and an antigen conjugated to an antibody which binds mouse DEC-205 having the amino acid sequence of SEQ ID NO: 3, wherein the antibody cross-reacts with human DEC-205. The amino acid sequence of SEQ ID NO: 3 corresponds to the full-length sequence of mouse DEC-205. Support for independent claim 40 can be found at least, for example, at page 5, lines 13-23; page 7, lines 1-12; page 10, line 20 through page 11, line 14; page 42, lines 24-31; page 55, line 30 through page 56, line 23; page 62, line 26 to page 63, line 15 and page 67, lines 15-21 of the specification as originally filed.

Support for independent claim 40 can also be found in the Substitute Sequence Listing submitted in the present application on December 22, 2005, which identifies the full length mouse DEC-205 sequence as SEQ ID NO: 3.

Support for the full length mouse DEC-205 sequence (SEQ ID NO: 3) also can be found in the parent application, U.S.S.N. 09/586,704, which is incorporated by reference in its entirety in the present application, U.S.S.N. 09/925,284. Additionally, support can be found in the Substitute Sequence Listing submitted in the present application on December 22, 2005, which identifies the full length mouse DEC-205 sequence as SEQ ID NO: 10.

Dependent claims 42-43 on appeal do not stand or fall together with independent claim 40, or with each other, because the scope of each dependent claim differs from the independent claim, and from each other. In particular, dependent claims 42-43 additional features not required by independent claim 40. Specifically, dependent claim 42 specifies that the immune stimulator is selected from the group consisting of a cytokine, a lymphokine, and an adjuvant. Support for dependent claim 42 can be found, at least, for example, in original claim 28 and at page 7 (lines 6-8); page 18 (lines 1-4); page 46 (lines 6-15) of the specification as originally filed. Dependent claim 43 specifies that the antigen is selected from the group consisting of a virus, a bacterium, a parasite, and a tumor. Support for dependent claim 43 can be found, at least, for example, in original claim 27, at page 7 (lines 5-6); and page 46 (lines 14-15) of the specification as originally filed. Accordingly, the scope and limitations of claims 42-43 differ from claim 40, and thus the inquiry as to whether these claims are properly enabled and sufficiently described also differs from claim 40.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants present the following issue for review:

1. Whether claims 26-28 and 35-43 are properly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

2. Whether claims 26-28 and 35-39 are properly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

3. Whether claims 26-28 and 35-43 are properly rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement.

VII. ARGUMENTS

A. Summary of Examiner's Rejection of Claims 26-28 and 35-45 Under 35 U.S.C. § 112, First Paragraph, as Failing to Comply with the Written Description Requirement

The Examiner has rejected claims 26-28 and 35-45 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that the specification does not provide adequate written description for the claimed invention because, while the specification discloses the full length sequence of murine DEC-205 protein, it only discloses a partial sequence for human DEC-205. The Examiner asserts that, because human DEC-205 is approximately 1800 amino acids in length, the recitation in the claim of a 30 or 25 amino acid sequence derived from human DEC-205 does not provide adequate written description of a molecule that is almost 1800 amino acids in length. The Examiner further asserts that the claims encompass antibodies that bind any immunogenic epitope on the approximately 1775 undisclosed amino acids of DEC 205, and that the term human DEC-205 presumably encompasses full length human DEC-205, as well as undescribed mutants and alleles of human DEC-205.

B. Appellants' Response

1. Each Independent Claim Requires Separate Consideration

Appellants respectfully disagree with the Examiner's rejection. As a preliminary matter, the scope of claims 26-28, 35-36, 38-40, and 42-43 varies and, as such, the assertions made by the Examiner are not equally applicable to all of these claims.

Specifically, contrary to the Examiner's opinion that the claimed antibody conjugates do not bind to any specific epitope of human DEC-205, claims 35-36 and 38-39 are drawn to antibody conjugates which do, indeed, bind to a particular epitope of human DEC-205, namely the C-terminal sequence (SEQ ID NO: 1).

Similarly, that the present specification teaches a partial human DEC-205 sequence is not a basis for rejecting claims 40 and 42-43, since these claims are drawn to a vaccine comprising an antigen conjugated to an antibody that binds to *full length murine DEC-205 protein* (SEQ ID NO: 3). Importantly, the full length sequence of

murine DEC 205 is explicitly provided in the present application as SEQ ID NO: 3. Moreover, because the antibody conjugates of claims 40-43 also cross-react with human DEC-205, the epitopes of human DEC-205 that the conjugates bind to are by definition, shared with (*i.e.*, cross-reactive with) murine DEC-205. As such, these epitopes are inherently provided as part of the full length murine DEC-205 sequence recited in the claims (SEQ ID NO: 3).

Finally, with respect to claims 26-28, drawn to a vaccine comprising an antigen conjugated to an antibody that binds to human DEC-205 protein comprising the partial amino acid sequence of SEQ ID NO: 1, the fact that Applicants' specification does not recite the full length human DEC-205 sequence, or variants of the sequence, does not *de facto* mean that the pending claims fail to comply with the written description requirement. It is well-established that the written description standard is not a bright line test, but instead takes into consideration a number of different factors. As discussed in detail below, Applicants' disclosure of the partial human DEC-205 sequence and the full length murine DEC-205 sequence, in combination with knowledge available in the art, are sufficient to demonstrate to one of ordinary skill that Applicants had possession of the claimed invention, *i.e.*, an antibody vaccine conjugate directed to human DEC-205 protein, at the time the present application was filed.

2. The Disclosure of a Fully Characterized Antigen Satisfies the Written Description Requirement

The Written Description requirement may be satisfied if the disclosed function of the claimed invention (*e.g.*, antibody binding) sufficiently correlates to a particular, known structure. Specifically, the Federal Circuit in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004) concluded that "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."

Claims 40 and 42-43 are drawn to a vaccine comprising an immune stimulator and an antigen conjugated to an anti-murine DEC 205 antibody that ***binds to murine DEC-205 protein*** (SEQ ID NO: 3) and cross-reacts with human DEC-205. As discussed above, the full length sequence of murine DEC-205 is explicitly provided in the present application as SEQ ID NO: 3. As such, the antibodies encompassed by

claims 40 and 42-43, which bind murine DEC-205 protein, clearly meet the written description standard set forth in *Noelle v. Lederman.*

Claims 26-28 are drawn to a vaccine comprising an immune stimulator and an antigen conjugated to an anti-human DEC 205 antibody or an anti-murine DEC-205 antibody that ***is reactive with a human DEC-205 protein,*** wherein the human DEC-204 protein comprises an amino acid sequence set forth in SEQ ID NO:1. Claims 35-36 and 38-39 are drawn to a vaccine comprising an immune stimulator and an antigen conjugated to an anti-human DEC 205 antibody (claim 35) or an anti-murine DEC-205 antibody (claim 36) that is ***reactive with SEQ ID NO:1*** (*i.e.*, the C-terminal sequence of human DEC-205). Given that the conjugates of claims 26-28, 35-36 and 38-39 cross-react with human DEC-205 (or a partial sequence thereof), the epitopes of human DEC-205 that the conjugates bind to are thus, by definition, shared with (*i.e.*, cross-reactive with) murine DEC-205. As such, these epitopes are inherently provided as part of the full length murine DEC-205 sequence (SEQ ID NO:3).

3. The Structure and Function of Human DEC-205 Correlates to the Structure and Function of Mouse DEC-205 Protein

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, *e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003) and *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Further, as originally articulated by the Federal Circuit in *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), and recently affirmed in *Carnegie Mellon University v. Hoffman-La Roche*, 541 F.3d 1115 (Fed. Cir. 2008), a claim to a genus satisfies the written description requirement when its accompanying specification either (1) defines by sequence a representative number of its members falling within the scope of the genus or (2) when its accompanying specification defines the structural features common to a substantial portion of the genus.

In the present case, the structure and function of human DEC-205 clearly correlates to that of mouse DEC-205, the characteristics of which (including full-length sequence) are described in detail in the present disclosure. Specifically, human and murine DEC-205 share approximately 90% amino acid homology, and both play the same role in antigen internalization, processing and presentation. Accordingly, the fact

that Appellants provide an in-depth characterization of mouse DEC-205, including its full-length sequence, which correlates to human DEC-205, as well as a partial (C-terminal) amino acid of human DEC-205, provides further descriptive basis for fully meeting the Written Description requirement.

In sum, the teachings set forth in Appellants' specification with respect to mouse DEC-205 and its structural and functional correlation with human DEC-205, satisfy the written description standard established by the Federal Circuit (*e.g.*, *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991), *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *Carnegie Mellon University v. Hoffman-La Roche*, 541 F.3d 1115, and *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004)) and demonstrate possession of the claimed invention.

4. The Descriptive Text Needed to Satisfy the Written Description Standard Must be Considered in Relation to the Scientific Knowledge in Existence at the time of the Invention, the Skill in the Art, and Correlation of a Disclosed Function to a Known Structure

The mere fact that Appellants' specification does not recite the full length human DEC-205 sequence does not alone mean that any of the claims on appeal fail to comply with the written description requirement. Indeed, the standard for meeting the written description requirement and showing possession of the claimed invention, as articulated by *Capon v. Eshhar*, differs for every patent specification depending upon a number of factors. These factors include the scientific knowledge in existence at the time of the invention, the skill in the art, the predictability of the claimed subject matter, and correlation of a described function to a known structure.

Appellants respectfully disagree with the Examiner's assertion that *Capon v. Eshhar* (418 F.3d 1349, 1357 (Fed. Cir. 2005)) "is not relevant to the claims under consideration." While the claims on appeal may differ from the claims on appeal in *Capon v. Eshhar*, the Court took considerable effort to lay out the underlying framework for determining written description in other cases moving forward, and to clarify that written description, like enablement, must be determined on a case by case basis. Appellants do not argue that the claims at issue in *Capon v. Eshhar* were the same as in the present case, rather that the written description standard articulated by the Court, when applied in the present case, is fully satisfied.

Specifically, as discussed further below, the maturity of the science and skill in the art at the filing date of the present invention were such that one of ordinary skill would recognize that Appellants were in possession of the full-length human DEC-205 protein, based on the partial sequences described in the specification, combined with the skill and predictability knowledge available in the art at the time of filing with respect to isolating full length proteins using partial sequences.

5 . Isolation and Cloning of Proteins, and Generation of Antibodies Were Highly Mature Technologies at the Time of the Present Invention

At the filing date of the present application (*i.e.*, in 1995), technologies for isolating, characterizing and cloning proteins were highly developed, as were technologies for generating antibodies against such proteins. Indeed, several well known techniques were available for cloning proteins, including human DEC-205, based on a given partial amino acid sequence of the protein (see, for example, page 20, line 30 through page 21, lines 1-19; as well as page 25, lines 25-31 through page 31, lines 1-16 of specification). Techniques for expressing cloned proteins (see, for example, page 31, lines 18-31 through page 35, lines 1-30 of the specification) and generating antibodies against the proteins also were well known (see, for example, page 42, lines 23-31 through page 45, lines 1-19, and particularly page 42, lines 28-31 of the specification). Accordingly, once armed with a partial amino acid (*i.e.,* a peptide derived from a given protein), it was well within the skill of the art to use these techniques to generate antibodies against such peptides, and to subsequently isolate the full-length protein from its natural source.

In fact, Appellants specifically showed this in relation to full-length mouse DEC-205, which they successfully isolated and characterized from whole murine thymus using mAb NLDC-145, an anti-mouse DEC-205 antibody (see pages 62-63 of specification). Additionally, Appellants successfully raised antibodies against N-terminal peptides from mouse DEC-205 protein (see, for example, page 62, lines 26-32 and page 63, lines 1-15 of the specification).

Similarly, the partial human DEC-205 sequence provided in the present disclosure (SEQ ID NO.:1) provides the ability to isolate and characterize full-length human DEC-205 protein. For example, it was well within the skill of the art to have generated antibodies against this partial sequence, and, in turn, to have isolated and sequenced the full-length human DEC-205 protein.

Indeed, as described in the Declaration by Dr. Michel Nussensweig (Exhibit A), the cloning techniques and techniques for generating antibodies described in the specification were ultimately successfully used to clone and isolate human DEC-205, and to produce antibodies against full-length human DEC-205. This provides clear evidence that Appellants were in fact indeed in possession of the claimed invention based on the descriptive text provided within the four corners of Appellants' originally filed disclosure.

C. Summary of Examiner's Rejection of Claims 26-28 and 35-39 Under 35 U.S.C. § 112, First Paragraph, as Failing to Comply with the Written Description Requirement

The Examiner has rejected claims 26-28 and 35-39 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that there is no support in the specification for a human DEC-205 protein comprising an amino acid sequence as set forth in SEQ ID NO.:1. The Examiner further asserts that, although the specification teaches that SEQ ID NO.:7 is a peptide derived from human DEC-205, there is no support for a human DEC-205 protein comprising the peptide, wherein the molecule could have any amino acids in association with the aforementioned sequences recited in the claim.

D. Appellants' Response

As an initial point, it is unclear to Applicants based on the Examiner's comments what the distinction is between the former 35 U.S.C. § 112, first paragraph, rejection of claims 26-28 and 35-45 for lack of written description (discussed above in Part A), and the present § 112, first paragraph, rejection of claims 26-28 and 35-39 for lack of written description. Indeed, both rejections appear to be based on the same premise, *i.e*, that the claims lack written description because the specification teaches a partial human DEC 205 sequence. Applicants note, however, that the former rejection has been applied to claims 26-28 and 35-45, whereas the present rejection has been applied only to claims 26-28 and 35-39.

Accordingly, with respect to claims 35-36 and 38-39 on appeal, Applicants again respectfully note that these claims are drawn to a vaccine that employs antibody conjugates defined as binding to a *particular* epitope on human DEC 205, the sequence of which is explicitly taught in the application (SEQ ID NO: 1, not SEQ ID NO: 7, as

noted by the Examiner). Therefore, the Examiner's assertion that the specification fails to provide support for a human DEC 205 protein comprising the partial sequence of SEQ ID NO: 1 does not provide a basis for rejecting claims 35-36 and 38-39 for lack of written description.

Moreover, for the reasons discussed above in subsection B, Applicants respectfully submit that the specification does indeed provide adequate written description for claims drawn to antibody vaccine conjugates direct to human DEC 205 protein comprising SEQ ID NO: 1, as recited in claims 26-28. Again, the mere fact that the disclosure teaches partial sequences for human DEC 205 does not alone mean that claims covering antibody conjugates which bind to human DEC 205 comprising such sequences lack written description. Indeed, whether claims 26-28 comply with § 112, first paragraph, depends on a variety of factors, as discussed above in relation to the previous rejection (subection B). When applied to claims 26-28, the teachings in Applicants' specification combined with the skill and knowledge available in the art at the time the present application was filed, as well as the correlation between murine and human DEC-205, clearly demonstrate that Applicants possessed the vaccine conjugates recited in claims 26-28.

As previously discussed in detail, Applicants teach the partial C-terminal sequence of human DEC-205 (SEQ ID NO: 1). Based on this partial amino acid sequence, it was well within the skill of the art to have generated antibodies against this peptide, and to have predictably isolated the full-length protein and variants thereof from their natural source. In fact, the maturity of the science and skill in the art at the time of the invention were such that those of ordinary skill in the art were routinely obtaining full-length proteins based on partial amino acid sequences, as well as predictably obtaining antibodies against such full-length proteins. This is specifically attested to in the Declaration submitted by Declaration by Dr. Michel Nussenzweig (Appendix B). Further, the fact that Applicants provide an in-depth characterization of mouse DEC-205, including its full-length sequence, which correlates to human DEC-205, provides further basis for fully meeting the Written Description requirement.

In sum, for at least the foregoing reasons, claims 26-28, 35-36, and 38-39 fully comply with 35 U.S.C. § 112, first paragraph.

E. Summary of Examiner's Rejection of Claims 26-28 and 35-45 Under 35 U.S.C. § 112, First Paragraph, as Lacking Enablement

The Examiner has rejected claims 26-28 and 35-45 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner is of the opinion that the specification fails to disclose how to use the presently claimed methods for the in vivo treatment of disease in humans. The Examiner further asserts that "there is no disclosure in the specification of any in vivo evidence in any model wherein the claimed invention is used as a vaccine or tumor vaccine."

F. Appellants' Response

Applicants respectfully traverse this rejection for at least the reasons set forth below.

(1) Enablement of Composition of Matter

MPEP 2164.02 provides that "***any enabled use*** that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use" (emphasis added). Accordingly, as applied to the present case, the claimed vaccines are clearly enabled. Specifically, in addition to *in vivo* immunotherapy, the claimed vaccines also are at least enabled for ***in vitro*** uses, such as testing, evaluating, and/or comparing the function, *e.g.*, antigen presentation, of DEC-205 receptors. In this regard, it is important to note that the present claims are drawn to vaccines conjugates (*i.e.*, compositions of matter), not to specific *in vivo* uses, although Applicants maintain that such *in vivo* uses also are fully enabled.

Moreover, as discussed below, working examples are not required for enablement under 35 USC 112, first paragraph. Rather, the disclosure of working examples supporting a claimed invention is only one factor to be considered in determining whether the invention is enabled, and is not solely determinative of the issue.

(2) In Vivo Data or Working Examples Are Not a Necessary Requirement for Enablement

In response to the Examiner's suggestion that working examples are required to satisfy the enablement standard, Applicants respectfully note that compliance with the

enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether *in vivo* data or working examples are provided in the specification (M.P.E.P. § 2164.02). This is particularly true for composition of matter claims, such as those in the present application. In fact, the specification need not contain *in vivo* data or working examples if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)) and, importantly, ***if one of ordinary skill in the art would reasonably accept the supporting disclosure as being enabling based on the teachings and/or data that is provided*** (*In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)). In the present case, this standard is satisfied, notwithstanding the fact that the claims are clearly enabled for *in vitro* uses as well.

Moreover, contrary to the Examiner's assertion that the present specification fails to provide "appropriate evidence as to how the instant invention could be used for the *in vivo* treatment or prevention of disease in humans," the specification does indeed provide sufficient teachings, when combined with the knowledge in the art at the time the present application was filed, for one of ordinary skill to have made and used the claimed conjugates without undue experimentation, ***as well as working data which would provide one or ordinary skill a more than reasonable basis for accepting that the disclosure is enabling for in vitro and in vivo uses***.

For example, the specification provides multiple examples which unequivocally demonstrate *in vitro* that DEC-205 receptors are internalized after being bound by anti-DEC-205 antibodies (see, *e.g.*, pages 69-70). Applicants further exemplify the successful presentation of rabbit IgG-peptide/MHC complexes to T cell clones using rabbit-anti-DEC-205 antibodies (see, *e.g.*, pages 69-71). Such data, provide evidence that the claimed vaccines are fully enabled for *in vivo* use, and would support a reasonable conclusion by one of ordinary skill in the art that this was the case.

Moreover, further evidence that the claims are fully enabled for *in vivo* vaccine therapy is provided by the post-filing *in vivo* working examples (conducted in mouse models) described in US 20020187131. Specifically, the *in vivo* experiments using murine models described in US 20020187131 successfully demonstrated that (1) antigen delivered to dendritic cells *in vivo* induces persistent T cell activation (see page 37, line 14 through page 38, line 7, of US 20020187131), (2) the absence of persistent T cell activation in mice injected with an anti-DEC-205 antibody fused to hen egg

lysozyme (αDEC/HEL) is not due to a lack of antigen and, therefore, that targeting of antigen to DEC-205 causes persistent T cell activation (see page 38, lines 7-16, of US 20020187131), and (3) techniques for assessing dendritic cell function in mice receiving multiple doses of an anti-DEC-205 antibody fused to hen egg lysozyme (αDEC/HEL) (see page 38, line 18 through page 39, line 3, of application number 09/925,284). This *in vivo* data proves that the *in vitro* data described in Appellants' specification correlates with *in vivo* efficacy and provides further evidence that the claimed conjugates are fully enabled.

Moreover, as discussed below, mouse models have long been accepted in the field as being reasonably correlative of human treatment. While clinical studies in humans may ultimately be required to establish human treatments and therapeutic regimens, ***it is readily acknowledged in the art that the basic molecular principle behind a particular method of treatment is often first identified in a murine model.*** As supported by the examples in US 20020187131, Appellant's specification fully enables the production and use of the claimed vaccine conjugates for developing *in vivo* immune tolerance by targeting an antigen to dendritic cells using anti-DEC-205 antibodies. The discovery of this molecular principle of tolerance was a typical and pivotal first step in establishing a pervasive concept for disease treatment.

(3) Level of Predictability in the Art

The Examiner further asserts that *in vivo* treatment using the presently vaccine conjugates is unpredictable in view of the teachings provided in the prior art. Applicants respectfully traverse this rejection.

From the outset, Applicants again note that the present claims are drawn to vaccine conjugates (*i.e.*, compositions of matter), not to specific *in vivo* uses. Therefore, the invention is enabled as long as it has at least one enabled use. As exemplified in the present application, and described in detail above, multiple examples are provided in the present specification which predictably show the use of the claimed vaccines for testing, evaluating, and/or comparing the function, *e.g.*, antigen presentation, of DEC-205 receptors. Therefore, the invention is clearly enabled for *in vitro* uses, notwithstanding in vivo uses.

Moreover, Applicants' respectfully disagree with the Examiner's statements regarding the cited reference, Schjetne *et al.* (*J. Immunol.* 2007 Apr 1;178(7):4169-76). The Examiner maintains that it is "unpredictable whether human disease can be treated

via enhancing tolerance to a disease antigen" in view of Schjetne *et al.* The Examiner relies on Schjetne *et al.* as teaching that "DEC205 antigen conjugates administered in vivo require CD40 ligation in vivo in order to induce an immune response (see page 4169, second column, first paragraph)" and concludes that "the claimed invention would not be expected to induce an immune response" or to treat disease in humans "because it lacks an agent that causes CD40 ligation." Further, with respect to the use of the invention as a tumor vaccine, the Examiner asserts that Schjetne *et al.* "teach that even in the presence of CD40 ligation...tumor vaccines would be unsuitable for treating tumor bearing animals (see page 1475, first page, last paragraph)."

Appellants respectfully disagree. Contrary to the Examiner's suggestion, Schjetne *et al.* do not support a lack of predictability for the presently claimed vaccine conjugates targeted to DEC-205. Indeed, as explained by Schjetne *et al.*, the lack of immune response they observed targeting antigen to CD40 receptor was likely due to the fact that CD40 is not an efficient endocytic receptor. In contrast, the presently claimed target receptor, DEC-205 is an ***efficient endocytic receptor***, as stated by the authors. Specifically, Schjetne *et al.* state:

> ... the requirement for a physical linkage between the Ag and the maturation signal in the present experiments superficially appears to contradict recent in vivo studies demonstrating induction of long-lasting T cell responses even when anti-CD40 mAb was not linked to the Ab-Ag fusion protein ... The difference might be explained by the fact that in the latter case, the recombinant Ab-Ag fusion was targeted to **DEC205, an efficient endocytic receptor expressed on DC** ..., but lacking the ability to induce a maturation signal.. Thus, **linkage between the CD40-targeting unit and the Ag might only be required if the Ag is otherwise inefficiently endocytosed by APC, as was the case in the design of the present study** (emphasis added).

Moreover, with respect to the value of using animal models as a preliminary step in establishing a concept for disease treatment in humans, Applicants refer to the publications by (1) Tufveson *et al.* (Immunol Rev. 1993 Dec;136:99-109), and (2) Mestas *et al.* (*J Immunol.* 2004 Mar 1;172(5):2731-8).

Specifically, while Tufveson *et al.* (Immunol Rev. 1993 Dec;136:99-109) suggest that data from small animal models should not be the *sole basis* for "clinical decision making"... the authors also state that "it is evident that animal experiments to support modes of clinical action are warranted" (see page 101). Similarly, while Mestas *et al.* point out that mice and humans have obvious differences that "should be taken into account when using mice as preclinical models of human disease," the

authors teach that "[***m]ice are the experimental tool of choice for the majority of immunologists and the study of their immune responses has yielded tremendous insight into the workings of the human immune system***" and that "***mice are the mainstay of in vivo immunological experimentation and in many respects they mirror human biology remarkably well***" (see page 2731).

Further, contrary to the Examiner's suggestion that *in vivo* treatment using the presently conjugates is unpredictable in view of teachings available in the art, Applicants respectfully note that there is ***substantial evidence*** in the art to demonstrate that a molecular principle ***can*** be predictably applied to the development of human therapeutics, once a principle has been identified and tested, for example, *in vitro* and/or an animal disease model (*e.g.*, an *in vivo* murine disease model). For example, Tysabri, an anti-VLA4 treatment for multiple sclerosis in humans, was presaged by Lawrence Steinman's anti-VLA studies of experimental allergic encephalomyelitis (EAE) in mice; see, for example, Yednock *et al.* (1992) *Nature* 356: 63-66, which concluded that "... therapies designed to interfere with alpha 4 beta 1 integrin may be useful in treating inflammatory diseases of the central nervous system, such as multiple sclerosis." Similarly, Copaxone treatment for multiple sclerosis in humans, was presaged by Ruth Arnon's and Michael Sela's studies with copolymers in EAE in mice and the discovery of synthetic peptides as model antigens; see, for example, Teitelbaum D. *et al.* (1971) *Eur. J. Immunol.* 1: 242-248 which concluded that "[i]n its suppressive activity (the copolymer), it is as effective as the brain encephalitogen itself and thus may be of help both in studies of the mechanism of EASE and as a potential suppressive agent for EAE and other diseases of a similar nature." Additionally, FDA approved IL-2 treatment of cancer in humans was presaged by Steve Rosenberg's studies of mouse melanoma rejection in mice; see, for example, Rosenberg *et al.* (1985) *J. Exp. Med.* 161: 1169-1188, which concluded that "[t]he ready availability of high doses of recombinant human IL-2, and the demonstration of antitumor effects seen in animal models have led us to the initiation of the clinical trials of recombinant IL-2 in humans." Finally, CTLA-4 blockade, for which FDA approval is currently being sought as a new weapon in the treatment of cancer in humans, was presaged by Jim Allison's studies of anti-CTLA treatment of mouse tumors and the discovery of CTLA-4 as a counter-receptor for costimulatory B7 molecules in mice; see, for example, Leach *et al.* (1996) *Science* 271: 1734-1736, which concluded that "[t]hese results

suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effect immune responses against tumor cells."

These are but a few examples evidencing that a molecular principle ***can*** be predictably applied to the development of human therapeutics. Accordingly, it is clear that *in vivo* mouse models of experimentation are widely accepted as playing a key, initial role in the establishment of methods and therapeutics for treating human disease. The *in vitro* data described in Appellants' specification alone would have led one of ordinary skill in the art to believe that the claimed conjugates are fully enabled for *in vivo* use. However, the post-filing data set forth in the US 20020187131 confirms that the data described in Appellants' specification does, indeed, correlate with *in vivo* efficacy. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 112, first paragraph.

VIII. APPENDIX OF CLAIMS

A copy of the claims involved in the present appeal is set forth in Appendix A.

IX. CONCLUSION

In view of the above arguments, Appellant urges the Examiner and the Board to reconsider and withdraw the current rejections and to pass the claims to allowance.

Appellant believes that the pending application is in condition for allowance. If additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. RUJ-001CNRCE2 from with the undersigned is authorized to draw.

Dated: January 25, 2011

Respectfully submitted,

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APPENDIX A: CLAIMS

26. **(Previously Presented)** A vaccine for inducing an immune response comprising an immune stimulator and an antigen conjugated to an anti-human Dendritic and Epithelial Cell 205 (DEC-205) antibody or an anti-murine DEC-205 antibody reactive with a human DEC-205 protein, said human DEC-205 protein comprising an amino acid sequence as set forth in SEQ ID NO: 1.

27. **(Previously presented)** The vaccine of claim 26, wherein the antigen is selected from the group consisting of a virus, a bacterium, a parasite, and a tumor.

28. **(Previously Presented)** The vaccine of claim 26, wherein the immune stimulator is selected from the group consisting of a cytokine, a lymphokine, and an adjuvant.

35. **(Previously Presented)** A vaccine for inducing an immune response comprising an immune stimulator and an antigen conjugated to an anti-human Dendritic and Epithelial Cell 205 (DEC-205) antibody, wherein the antibody is reactive with the amino acid sequence as set forth in SEQ ID NO: 1.

36. **(Previously Presented)** A vaccine for inducing an immune response comprising an immune stimulator and an antigen conjugated to an anti-mouse Dendritic and Epithelial Cell-205 (DEC-205) antibody, wherein the antibody is reactive with the amino acid sequence as set forth in SEQ ID NO: 1.

38. **(Previously Presented)** The vaccine of claim 35 or 36, wherein the immune stimulator is selected from the group consisting of a cytokine, a lymphokine, and an adjuvant.

39. **(Previously Presented)** The vaccine of any one of claims 26, 35, or 36, wherein the antigen is selected from the group consisting of a virus, a bacterium, a parasite, and a tumor.

40. **(Previously Presented)** A vaccine for inducing an immune response

comprising an immune stimulator and an antigen conjugated to an antibody which binds mouse Dendritic and Epithelial Cell 205 (DEC-205) having the amino acid sequence of SEQ ID NO: 3 , wherein the antibody cross reacts with human DEC-205.

42. **(Previously Presented)** The vaccine of claim 40, wherein the immune stimulator is selected from the group consisting of a cytokine, a lymphokine, and an adjuvant.

43. **(Previously Presented)** The vaccine of claim 40, wherein the antigen is selected from the group consisting of a virus, a bacterium, a parasite, and a tumor antigen.

APPENDIX B: EVIDENCE

Appendix B is a copy of the Declaration by Dr. Michel Nussensweig, which was entered by the Examiner in conjunction with the Amendment and Response filed by Appellants on January 3, 2005.

Appendix C is a copy of Guo *et al.* (Hum Immunol. 2000 Aug; 61(8):729-38), which was referenced in the Declaration by Dr. Michel Nussensweig and cited in an Information Disclosure statement (dated December 27, 2005) that was considered and initialed by the Examiner on March 23, 2006.

APPENDIX C: RELATED PROCEEDINGS

An Appeal Brief was filed in the Continuation-in-Part application, U.S.S.N.: 09/925,284 (filed August 9, 2001).